UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 29 1998

MEMORANDUM

SUBJECT: Fipronil - Review of Incident Reports for Three Products

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Action Requested: Review incident reports for three fipronil products used for flea and tick control, Frontline® Spray Treatment (65331-1), Top Spot™ for Cats (65331-2) and Dogs (65331-3) and registrant's analysis of adverse effects data.

Recommendations:

1. Comparing rates of suspected adverse events submitted by the registrant after 1996 and 1997, it appears there has been an increase in the rate for dogs exposed to Top Spot™ for Dogs. However, the rate is still extremely low and should not affect the conversion of the time limited registration to an unlimited registration. It is recommended that the registrant submit similar rates for all three Frontline products at the end of 1998 to monitor the trend in suspected adverse events. See a more detailed discussion under **Discussion/Recommendations** on page 5.

2. The severity of the dermal reactions seen in some dogs and cats is of concern. The label statement under HAZARDS TO DOMESTIC ANIMALS, "Pets may experience some temporary irritation at the site of product application", does not adequately describe the severe reactions. The registrant should propose label revisions that provide instructions to pet owners on how to remove

the product if the irritation persists beyond a certain time period and about using the product in the future on animals that have demonstrated sensitivities.

3. Based on the incident data to date, the Bichon Frise breed may be especially sensitive to dermal irritation with Top Spot™. It is recommended that the registrant submit individual incident reports on this breed rather than including them with the summary reports, which will be required as of June 16, 1998, under the final 6(a)(2) Rule.

4. Misuse of the products on rabbits or instillation into the ears for the treatment of ear mites should be monitored. If such misuse continues, the label should be revised to warn against these practices.

Background

In a previous review, the incident reports from the time of registration until March 17, 1997 for the three fipronil veterinary products, Frontline® Spray Treatment (65331-1), Top Spot™ for Cats (65331-2) and Dogs (65331-3), were evaluated. See April 16, 1997 Memo from Virginia Dobozy to Richard Griffin (HED) and Rick Keigwin (RD). At that time, the following number and type of incidents were reported to the OPP Incident Data System for the three fipronil products.

Type of Reaction	Frontline Spray		Top Spot for Cats		Top Spot for Dogs	
	Cats	Dogs	Cats	Dogs	Cats	Dogs
Dermal irritation	1	10	21	-	-	30
Systemic reaction	9	4	13	-	-	2
Death	-	-	1	-	-	-

Based on that review, the following recommendations were made:

1) The number and type of adverse reactions were not excessive or unexpected. Most of the incident reports involved skin irritations which were reported in the studies done prior to registration. The labels for Top Spot™ state that pets may experience some temporary irritation at the site of product application.

2) There were three reports of systemic reactions when Frontline® Spray was misused and instilled into cats' ears. If reports of this misuse continue, label revisions should be considered to warn against this practice.

It was additionally noted that a relatively large percentage (12.5%) of the adverse reactions were reported in Bichon Frise's, a relatively uncommon breed.

Review of Incidents from March 17, 1997 to April 13, 1998

Estimates of the number and type of adverse reactions reported to the OPP Incident Data System for the three fipronil veterinary products since March 17, 1997 are as follows.

Type of Reaction	Frontline® Spray		Top Spot™ for Cats		Top Spot™ for Dogs	
	Cats (10)[a]	Dogs (8)[a]	Cats (101)[a]	Dogs	Cats	Dogs(215)[a]
Dermal irritation	-	7	74	-	-	183
Systemic reaction	9	3	27	-	-	32
Death[b]	6	3	10	-	-	17

a Number of animals affected; more than one type of reaction could be reported for each animal.
b If dermal irritation or systemic reactions were observed prior to death, they were also counted in these categories.

There were also four rabbits treated with Top Spot™ for Cats; most developed neurological signs of toxicity.

The majority of the deaths were investigated and the cause of death attributed to a reason other than fipronil exposure. In some cases where the cause was not identified, a necropsy was not conducted, although the registrant offered to cover the cost. One adult cat and three kittens died after they were exposed to Frontline Spray and were then confined in a carrier or under blankets, respectively. The inhalation of the product vapors may have contributed to these deaths; no necropsies were done. Follow-up results for two incidents are still pending. In I005336, the New Jersey EPA forwarded a preliminary investigation into the report of one dog which died and another which was blinded. In I005627-022 (complaint 9717074), a 9 month-old Siberian Husky was found dead 48 hours after application of the product. Results of the histopathology are pending.

As demonstrated in the above table, the majority of the adverse reactions in both cats and dogs were of a dermatological nature. In cats treated with Top Spot™, there was a spectrum of reactions in the incident reports from simple irritation and/or hair loss at the application site to severe moist dermatitis and ulcerated areas that extended beyond the application site. However, it is the general impression of this reviewer that dogs are more severely affected than cats. For dogs, there was a spectrum of reactions similar to cats. However, pruritis seemed to be more frequently reported and the areas affected more extensive. Several veterinarians described the skin as appearing to be "chemically burned". Skin sloughing also occurred more frequently in dogs. Many animals had multiple monthly applications before the reaction was observed. In many instances, the registrant attributed the reaction to individual sensitivity. Advise given by the registrant (from the incident reports) included bathing (even though the label states that the product remains effective after bathing), treatment of the dermal lesions and use of Frontline Spray in the future. For both cats and dogs, there is a problem with differentiating the contribution of the fipronil products to the dermal effects and the contribution of the flea allergy dermatitis (FAD), if present. However, with

FAD, the majority of the lesions are on the lower back and hindquarters, whereas with the fipronil incidents most of the lesions at least originated with the site of application.

Review of Registrant's Analysis

Merial Limited submitted an analysis titled "Frontline® Products Reports of Suspected Adverse Events Analysis of Breed, Age and Sex Distribution of Dogs and Cats." A total of 344 reports received as of December 23, 1997 were analyzed according to breed, sex and age for each of the three products. Doses of product sold from product launch through September 30, 1997 are: 7.8, 16.4 and 5.2 million for Frontline® Spray, Top Spot™ for Dogs and Top Spot™ for Cats. The number of suspected adverse events (SAE) as a function of doses sold are 0.00029%, 0.00126% and 0.0022%, respectively, per million. According to the registrant's analysis, there were no breed, age or sex sensitivities that would warrant specific mention on Frontline product labels. The breeds with the largest percentage of reactions were Retriever (Golden): 7.7%; German Shepherd: 6.8%; and Retriever (No Desc.), mixed breed and Bichon Frise: all 5.3%. According to the American Kennel Club list of the most popular breeds for 1997, Labrador Retriever was number 1, German Shepherd number 3 and Golden Retriever number 4. It is not surprising that there are a large percentage of reactions in these breeds. However, the Bichon Frise is a relatively uncommon breed. Therefore, as noted in the previous review, it appears to be over-represented. It can be argued that this breed is especially susceptible to dermatological conditions, however other susceptible breeds, such as the West Highland White terrier, do not have an increased sensitivity to Frontline products.

Discussion/Recommendations

1. The rates of suspected adverse events proposed by the registrant are underestimates, given the denominator used for the calculations. The use of "doses sold" overestimates the amount of product actually used. Below is a comparison of the rates reported by the registrant based on doses sold through December 31, 1996 and December 23, 1997.

	December 31, 1996	December 23, 1997
Frontline® Spray	0.0004	0.00029
Top Spot™ for Cats	0.0011	0.00126
Top Spot™ for Dogs	0.0005	0.0022

It appears that there has been an increase in the rate for dogs exposed to Top Spot™ for Dogs. However, the rate of suspected adverse events is still extremely low and should not affect the conversion of the time limited registration to an unlimited registration. To monitor the trend with these products, it is recommended that the registrant submit similar rates for all three products at the end of 1998.

2. The severity of the dermal reactions seen in some dogs and cats is of concern. The label

statement under HAZARDS TO DOMESTIC ANIMALS, "Pets may experience some temporary irritation at the site of product application", does not adequately describe the severe reactions. The registrant should propose label revisions that provide instructions to pet owners on how to remove the product if the irritation persists beyond a certain time period and about using the product in the future on animals that have demonstrated sensitivities.

3. Based on the incident data to date, the Bichon Frise breed may be over-represented. It is recommended that the registrant submit individual incident reports on this breed rather than include them with the summary reporting which will be required as of June 16, 1998 under the final 6(a)(2) Rule.

4. Misuse of the products on rabbits or instillation of the products into the ears for treatment of ear mites should be monitored. If such misuse continues, the label should be revised to warn against these practices.